CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-036

CORRESPONDENCE

BEDFORD
LABORATORIES™

ORIG AMENDMENT
N/AM

September 29, 2000

MINOR AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **Minor Amendment**
Product: **Cisplatin for Injection, USP; 10 mg and 50 mg vials**
Cisplatin Injection; 1 mg/mL, 50 mL and 100 mL vials

Dear Sir/Madam,

We wish to amend our tentatively approved Abbreviated New Drug Applications, ANDA 74-713, for Cisplatin for Injection, USP, and ANDA 75-036, for Cisplatin Injection, 1 mg/mL, 50 mL and 100 mL vials, to address the deficiency cited in the Agency's letter of March 8, 2000 and April 4, 2000, respectively.

Bedford Laboratories™ has received a communication from indicating that the New Jersey District Office of the FDA has recommended approval to CDER for A copy of this communication is attached.

We trust this meets with your approval. If there are any questions or comments, please contact the undersigned at (440) 232-3320, ext. 3333.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

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BEDFORD
LABORATORIES™

July 24, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

RE: **ANDA 75-036/Gratuitous Amendment**
Product: **Cisplatin Injection; 1 mg/mL, 50 mL and 100 mL vials**

Dear Sir/Madame:

Bedford Laboratories™ wishes to amend the tentatively approved Abbreviated New Drug Application, ANDA 75-036, for Cisplatin Injection, to notify the Agency that Bedford Laboratories™ has amended this application with a Methods Validation Package, pursuant to the letter from the FDA, Laboratory Branch in Philadelphia, PA. As stated in this letter of April 4, 2000, this is a gratuitous amendment, as the samples provided for testing were not from the original exhibit lot. A new lot of Cisplatin Injection, 0832-60-209574, was manufactured and samples from that lot, as well as the executed lot record, are being provided to the laboratory and to the application.

We trust this meets with your approval. If there are any questions or comments, please contact the undersigned at (440) 232-3320, ext. 3333 or facsimile at (440) 232-2772.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

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ANDA 75-036

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, Ohio 44146

APR - 4 2000

Dear Sir:

This is in reference to your abbreviated new drug application dated December 23, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cisplatin Injection 1mg/mL, 50 mL and 100 mL vials.

Reference is also made to your amendment dated March 6, 2000.

We have completed the review of this abbreviated application and have concluded that the application is deficient and, therefore, not approvable under 21 CFR 314.125(b)(13) because the Center for Drug Evaluation and Research is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, and packaging or holding of the drug substance comply with current good manufacturing practice (CGMP) regulations.

Our conclusion is based upon the findings revealed during a recent comprehensive inspection of your drug substance supplier, eptember 7, 1999 to September 22, 1999, by representatives of the United States Food and Drug Administration. Upon review of this report and the inspectional observations noted during this inspection, we have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of this abbreviated application.

Until such time as you can demonstrate to the Agency that these CGMP-related issues associated with your drug product have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved.

You should amend this application when the CGMP-related issues have been satisfactorily resolved. Your amendment to this application submitted in response to this not approvable letter will be considered as a MINOR AMENDMENT provided that the amendment contains no significant additional information

necessary to remedy the CGMP problems, and includes a statement from a responsible corporate official certifying that your drug substance supplier has been found to be in compliance with CGMP and have been cleared for approval by representatives of the local FDA District Office. If, as a result of follow-up inspections related to these or other problems, it is necessary for you to significantly revise your procedures, controls or practices to correct your CGMP problems, then the amendment will be considered to represent a MAJOR amendment.

Please note that we are scheduling Methods Validation for your drug product in a FDA laboratory. Please provide samples promptly when contacted.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

4/3/00

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

March 6, 2000

BEDFORD LABORATORIES™

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

N/AM

RE: ANDA 75-036
Product: Cisplatin Injection; 1 mg/mL, 50 mL and 100 mL vials

Dear Sir/Madame:

Bedford Laboratories™ wishes to amend the tentatively approved Abbreviated New Drug Application, ANDA 75-036, for Cisplatin Injection, to notify the Agency that Bedford Laboratories™ wishes this application to be considered for final approval. This amendment provides a copy of the final order/judgement, revised labels and labeling, and a summary of the activity regarding the aforementioned application. FDA Form 356h is located in Attachment I.

Please refer to Attachment II for the copy of the opinion rendered in the Cisplatin litigation, Research Corporation Technologies v. Ben Venue Laboratories, Inc., Civil Action No. 3:97-2837 (GEB).

Located in Attachment III are the revised labels and labeling, revised in accordance with that of the reference listed drug. Also provided in this attachment are annotated side-by-side comparisons of the proposed labels and labeling versus the reference listed drug's labels and labeling.

The following is a summary of the activity regarding the Cisplatin Injection application, ANDA 75-036:

Event	Date
Application Filed under Bedford Laboratories™	December 23, 1996
Letter of Acceptance from FDA	February 26, 1997
Telephone Amendment	March 4, 1997
Patent Certification Notification to Bristol-Myers Squibb (BMS)	March 12, 1997
Patent Certification Notification to Research Corporation Technologies (RCT)	March 12, 1997
Notification to FDA Regarding Notification to BMS and RCT	March 24, 1997
Division of Bioequivalence Letter	May 20, 1997
Major Deficiency Received	May 15, 1997
District Status Notification from Cincinnatti	May 28, 1997
Major Amendment (Chemistry, Microbiology, Labeling	April 13, 1998
Facsimile Deficiency Received	September 21, 1998
Facsimile Amendment (Chemistry)	October 22, 1998

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Event	Date
Telephone Amendment	December 10, 1998
Telephone Amendment	December 10, 1998
Tentative Approval	December 29, 1998

Furthermore, Bedford Laboratories™ states that no changes have been made to the CMC section of ANDA 75-036 since the initial tentative approval of December 29, 1998.

We trust this meets with your approval. If there are any questions or comments, please contact the undersigned at (440) 232-3320, ext. 333 or facsimile at (440) 232-2772.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

SEP 2 2 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-036 APPLICANT: Bedford Laboratories, Inc.

DRUG PRODUCT: Cisplatin Injection, 1 mg/mL, 50 mL and 100 mL vials

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1.

2.

3.

4.

5.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The cGMP compliance of all facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Please be advised that samples of the drug product for methods validation will be requested at a later date once the testing issues have been resolved. A satisfactory evaluation is required to support this application. Inclusion of the current drug product specifications and analytical methods in a separate section of your amendment would be helpful.

3. Your response to the microbiological deficiencies submitted in your amendment is pending review.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-036 APPLICANT: Bedford Laboratories, Inc.

DRUG PRODUCT: Cisplatin Injection, 1 mg/mL, 50 mL and 100 mL vials

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please revise your specifications for Cisplatin drug substance to include specifications for individual and total metallic impurities based on the manufacturer's specifications.

2. Your intended production batch size is about 12 times the exhibit batch size for this submission. Please reduce it to no more than a ten fold increase. Please submit Master Batch Records for your new production batch size.

3. We have the following comments regarding the finished dosage form laboratory controls:

   a. Your specifications for total and individual other impurities are too high. We request specifications of [redacted] for individual and total other impurities, respectively. Please also validate your assay method to demonstrate that the method is sensitive enough at this level of impurities. Provide a representative chromatogram.

   b. Please include an APHA test and specification for monitoring the color of the drug product for its release.

   c. We note that you have provided a method description for the assay of [redacted] and [redacted] but failed to submit validation of these methods. Please submit appropriate validation for these methods in accord with the guidance of the USP <1225>.

4. We have the following comments regarding the stability of the drug product:

   a. Your specification for [redacted] is too high. We request a specification of

b. Your specifications for total and individual other impurities proposed for the shelf-life of the drug product are too high. We request specifications of for individual and total other impurities, respectively.

c. Please start monitoring the color in APHA color units for stability. Please submit a stability specification with respect of color of the drug product in APHA units.

d. Please be advised that long-term stability studies should be conducted on samples stored between 25° - 30°C or at 25 ± 2°C. Please revise your post-approval stability protocol and commitment.

e. Your exhibit batches fail the stability specifications proposed in this letter with respect to and unknown impurities based on the stability data generated under accelerated conditions. Full term data to the proposed expiration date is now necessary.

f. Please submit your revised stability specifications for both package sizes to include revisions proposed in this letter.

5. With respect to comments 3(a), 4(a) and 4(b), we may consider more relaxed specifications if you provide analytical data of the reference product (within expiry) to support them.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The cGMP compliance of all facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Please be advised that samples of the drug product for methods validation will be requested at a later date once the testing issues have been resolved. A satisfactory evaluation is required to support this application.

3. Microbiological and Labeling deficiencies will also need to be addressed in your reply.

4. A revised Patent Certification including the expiration date is needed for U.S. Patent No. 5,562,925.

5. You bioequivalence information is pending review.

Sincerely yours,

for Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Microbiology Comments to be Provided to the Applicant

ANDA: 75-036 APPLICANT: Bedford Laboratories
DRUG PRODUCT: Cisplatin Injection USP

Microbiology Deficiencies:

1. You have demonstrated that the subject drug product is not detrimental to the medium. However, the subject drug product is known to be antimicrobial in nature and a retentivity challenge was not performed. You should commit to perform challenge testing with any small vegetative bioburden bacterium, e.g., a pseudomonad, isolated from and demonstrated to grow in the subject drug product.

2. Submit recent revalidation data for of glass vials using . Similar data should be submitted for of rubber closures using stopper washers.

3. The original validation data submitted for the stoppers & filling equipment cycles obtained from experiments performed prior to 1991 and are acceptable. Please submit data summaries for the most recent revalidation experiments performed for these cycles.

4. You stated on page 162 of the application that the microbial integrity test data for the proposed container/closure system was currently being summarized. Please submit a copy of the summary report for review.

5. The subject drug products are packaged in multiple dose vials and must meet the requirements of USP 23 Chapter <51> Preservatives Effectiveness test. A data summary for the preservative challenge experiment performed using Cisplatin Injection should be submitted for review.

6. Please provide validation information, i.e., inhibition/ enhancement test data, for the subject drug product using the Kinetic Chromogenic LAL test method.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES".

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-036

MAY 20 1997

Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
270 Northfield Road
Bedford OH 44146

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Cisplatin Injection 1 mg/mL, 50 mL and 100 mL vials.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Ramanand M. Mhatre

for

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-036

Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
270 Northfield Road
Bedford, Ohio 44146

FEB 26 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Cisplatin Injection, 1 mg/mL, 50 mL and 100 mL vials

DATE OF APPLICATION: December 23, 1996

DATE OF RECEIPT: December 24, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please provide a side-by-side, qualitative and quantitative comparison of the formulation for your proposed drug product with that of the reference listed drug product in the bioequivalence section of your application. Please include this information in future submissions for parenteral drug products [21 CFR 320.22(b)(1)(i)&(ii)].

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 594-0370

Sincerely yours,

Jerry Phillips 2/26/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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December 23, 1996

Office of Generic Drugs
Center for Drug Evaluations and Research
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **Abbreviated New Drug Application**
Product: **Cisplatin Injection - 1 mg/mL, 50 mL and 100 mL vials**

Dear Sir/Madam:

In accordance with Section 505 (j)(1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories™ is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Cisplatin Injection, 1 mg/mL, 50 mL and 100 mL vials. Please note that the field copy is being sent directly to the FDA District Office in Cincinnati, Ohio.

The drug products subject to this application contains the information required by Section 505 (j)(2)(a)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office, and contains a copy of the package insert of the "listed drug's" (Bristol-Myers Squibb's Platinol-AQ®, NDA 18-057) as well as copies of the relevant pages of the **Approved Prescription Drug Products List with Therapeutic Equivalence Evaluations.**

In accordance with Title 21 CFR 320.22, Bedford Laboratories™ requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug products that are the subject of our application (Cisplatin Injection, 1 mg/mL, 50 mL and 100 mL vials). The drug products are solutions intended solely for intravenous administration and contain an active ingredient in the same solvent and concentrations as drug products that are the subject of an approved New Drug Application (Bristol-Myers Squibb's Platinol-AQ®, NDA 18-057).

Bedford Laboratories™ certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug products are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue Laboratories, Inc., signed statement is provided in Section IX (Manufacturing Facility) Subsection C (cGMP Certification).

Three copies of the analytical methods and method validations are enclosed in this package, also.

One copy of the Microbiological Validation, along with the drug products' specifications, stability

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protocols and the package insert is enclosed separately with this application. These drug products were aseptically filled.

If the Agency has any comments or further requests or if we could be of any assistance in your review, we welcome direct and immediate telephone contact at (216) 232-3320, ext. 218 or by facsimile (216) 232-2772.

Sincerely,
for Bedford Laboratories™

Robert V. Kasubick, Ph.D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.